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Original communication

Intra-individual and inter-individual variation in breath alcohol pharmacokinetics: The effect of short-term variation

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ABSTRACT

Ten male and 8 female students underwent serial breath alcohol concentration (BrAC) measurements on a CAMIC Datamaster on two consecutive occasions, early evening and again the following morning. Subjects were fasted for 6 h before receiving alcohol as white wine (12.5% by volume) at doses of 38–45 g for males and 26–37 g for females, consumed over 10 min. Specific individual doses were calculated individually from height and weight (according to the Forrest Method) to give target C_0 breath alcohol concentrations of 35 μg/100 ml breath in males and 31 μg/100 ml breath in females.

BrAC versus time curves were constructed for each subject and the values of peak BrAC (C_{max}), BrAC extrapolated at zero time (C_0), time taken to reach peak (T_{max}) and rate of elimination (β) were recorded directly from the curves. Values of C_0 taken from the BrAC–time curves varied widely, from 21 to 47 μg/100 ml on visit 1 and from 22 to 45 μg/100 ml on visit 2. Widmark Factors calculated from these C_0 values averaged 0.74 (range, 0.59–1.06) in males and 0.73 (range, 0.58–1.05) in females. Elimination rate was higher in the morning than evening in both males (7.4 versus 5.7 μg/100 ml/h) and females (6.9 versus 5.8 μg/100 ml/h). Elimination rates in males and females were not significantly different. Total body water, measured by electronic scales, averaged 58.7% (range, 56.6–63%) in males and 48.3% (range, 40.9–57.6%) in females. Widmark Factors calculated by various established mathematical methods were 0.73–0.77 in males and 0.61–0.64 in females.

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1. Introduction

Measurement of alcohol concentration in blood and breath is of major medico-legal importance with respect to drink-driving offences. Many of the more recent studies have involved measurement of breath alcohol concentration (BrAC) since this is the primary evidential specimen in most jurisdictions, its measurement is less invasive than blood sampling and because BrAC is thought to correlate well with blood alcohol concentration (BAC).[1] Breath samples have been found to show similar or lower variations than blood, both within and between subjects.[2]

Numerous factors may affect the rate and extent of alcohol absorption and its rate of elimination. Alcohol absorption rate is dependent upon the concentration of alcohol in the beverage consumed and upon carbonation of any mixers used.[3] Taking food with alcohol is known to both reduce the peak blood alcohol level achieved and enhance the rate of alcohol elimination.[4–7] Conversely, other studies demonstrated a slightly lower rate of alcohol elimination from breath after food.[8–10] The peak level achieved after food may only reach <70% of the level achieved after fasting.[10]

Yap found no significant differences in the common pharmacokinetic parameters amongst subjects given alcohol at various times of day apart from a slightly higher peak level; elimination rate was not found to differ.[11] Several studies have demonstrated significantly higher rates of alcohol elimination in females than in males.[12–16] Alcohol elimination has also been shown to be higher in heavy drinkers compared to moderate drinkers and higher in older subjects than younger ones.[16] Even breathing technique has been found to affect BrAC measurements.[17]

In Australia, alcohol drinking experiments can be performed when intoxicated drivers challenge blood alcohol concentration evidence based on mathematical assumptions relating to elimination rate.[18] For this reason, an individual's elimination rate may be

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determined experimentally several months after an alleged offence. The natural variability in breath alcohol elimination rate, both within and between subjects takes on great medico-legal significance in such situations.

Calculation of blood alcohol concentration (BAC) at any material time is usually based on the Widmark equation: $C_0 = A/p \cdot r$[19]where C_0 = theoretical BAC at zero time, assuming complete instantaneous absorption and distribution; A = amount of alcohol ingested (in grams); p = body weight (kg); r = Widmark Factor (W.F.), the fraction of the body mass in which alcohol would be present if it were distributed at concentrations equal to that in the blood;

The alcohol level at any given time is given by $Ct = C_0 - \beta \cdot t$, where C_t = BAC at time t minutes; β = elimination rate (mg/100 ml/h) and t = time elapsed in minutes.

Widmark's original research in 1932 proposed average values for the Widmark Factor (r) of 0.68 for males and 0.55 for females. These values are based on experiments on only 20 men and 10 women.[19] Use of mathematical models which include anthropological data such as sex, height, weight and build can be expected improve the estimation of Widmark Factor.[19]

In drinking experiments, the Widmark Factor (r) can be estimated by rearranging the Widmark equation since the alcohol dose is known and a value of C_0 can be extrapolated back from the linear portion of the experimental BAC or BrAC curve. At its simplest, use of the Widmark equation depends on knowledge of the subject's weight and sex and on how much alcohol was consumed at a former time. In forward calculations, where the BAC likely to be achieved following consumption of a known amount of alcohol is calculated, the principal factor contributing to error is the uncertainty concerning the volume of distribution or Widmark Factor. In retrograde or back calculations, where the BAC likely to have existed at an earlier time is estimated from a measured level, the principal factor contributing to error is the individual's rate of elimination. Back calculation of alcohol concentrations to the time of an offence have usually involved conversion of BrAC to BAC as elimination rates in breath have only recently been established.[15] However, the BAC/BrAC conversion factor (Q) is itself subject to great variations since Q appears to be inversely proportional to BrAC and dependent on the alcohol kinetic state of the person.[20] In the UK, where the legal limits for driving are 80 mg/100 ml blood and 35 μg/100 ml breath, the theoretical value of Q used in mathematical conversions would be 2286 (=80/0.035).

There are several competing variables which affect the rate of absorption, distribution and elimination of alcohol. The present study was designed to assess the effect of short-term variation on breath alcohol concentrations and BrAC–time curves in student volunteers.

2. Materials and methods

2.1. Subjects and conditions

Subjects were student volunteers who were given a full written explanation of the procedure and asked to complete a detailed health questionnaire which included details of any medical conditions, prescribed drugs, and normal drinking and smoking habits. If deemed suitable, informed consent for participation was obtained from each subject. The experimental work was carried out in 2008–09 with ethical approval granted by the Tayside Committee on Medical Research Ethics. Anthropological data for each subject is given in Table 1.

2.2. Administration of alcohol dose

Ten male and 8 female subjects underwent serial BrAC measurement on two closely consecutive occasions, firstly in the evening and again the following morning. Volunteer subjects were asked to refrain from food and drink for a minimum of 6 h prior to attending each experiment. A small drink of water was allowed within the fasting period, if required. On the first visit weight and total body water (%) were recorded on electronic body composition scales (Tanita BC-570 Innerscan Family Body Composition Monitor). Height was measured to within 1 cm. Subjects completed a questionnaire detailing their usual drinking habits and recent alcohol, food and cigarette consumption. A breath sample was then screened for alcohol to ensure subjects were free of alcohol prior to commencement.

On each visit, fasted subjects were given an ethanol loading dose as white wine of 12.5% alcohol by volume (abv). The loading dose was calculated using Forrest's method[21] to give a target BAC of 80 mg/100 ml (equivalent to 35 μg/100 ml breath) in males and 72 mg/100 ml (equivalent to 31 μg/100 ml breath) in females.

For each subject, the alcohol dose was calculated by rearranging the Widmark equation:

Table 1
Anthropological data of male and female subjects.

	Age (years)	Weight (kg)	Height (m)	BMI	% TBW (scales)	Alcohol dose (g)
M1	21	75.4	1.86	21.8	56.6	45.4
M2	22	74.3	1.78	23.5	57.6	43.5
M3	21	74.2	1.85	21.7	61.7	44.7
M4	21	79.2	1.71	27.1	56.8	43.5
M5	21	71.9	1.67	25.8	56.9	40.5
M6	21	74.4	1.81	22.7	61.1	44.1
M7	21	65.7	1.71	22.5	63	39.2
M8	21	70	1.79	21.8	58.9	41.5
M9	22	76.7	1.65	28.2	58	42.2
M10	23	66.7	1.62	25.4	56.7	37.8
Mean (range)	21.4 (21–23)	72.9 (65.4–79.2)	1.75 (1.62–1.86)	24 (21.7–28.2)	58.7 (56.6–63)	42.3 (37.8–45.4)
F1	19	51.2	1.66	18.5	57.6	26.3
F2	22	85.8	1.8	26.5	44	37.4
F3	19	64.8	1.71	22.2	51.6	31
F4	18	54	1.7	18.7	56	27.7
F5	20	69.2	1.65	25.4	45.3	30.9
F6	49	72.2	1.68	25.6	40.9	32.1
F7	24	68.4	1.58	27.4	47.2	29.2
F8	24	72.2	1.6	28.2	43.8	30.2
Mean (range)	24.4 (18–49)	67.2 (51.1–85.8)	1.67 (1.58–1.8)	24 (18.5–28.2)	48.3 (40.9–57.6)	30.6 (26.3–37.4)

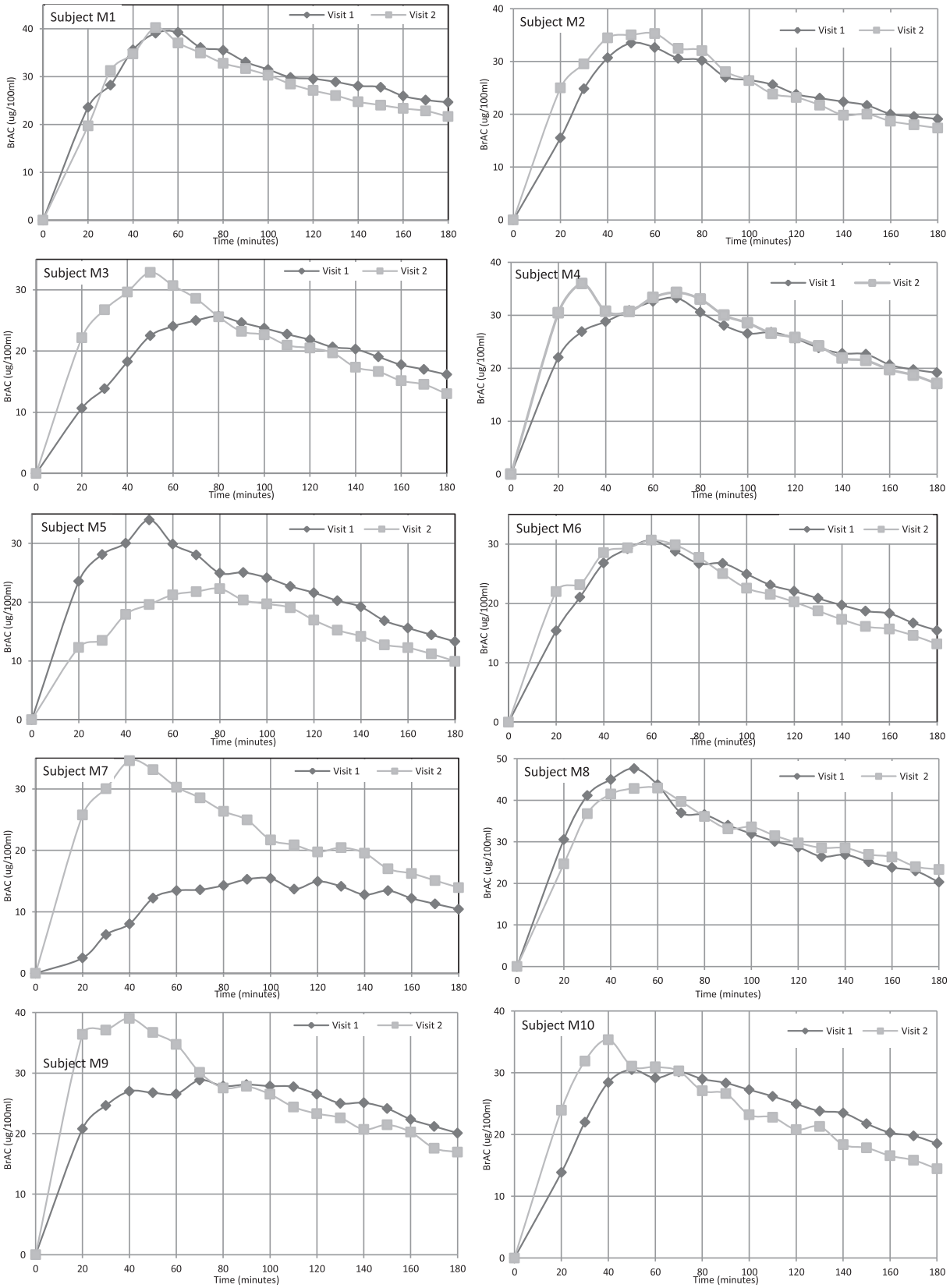

Fig. 1. Breath alcohol concentration–time curves for 10 male subjects.

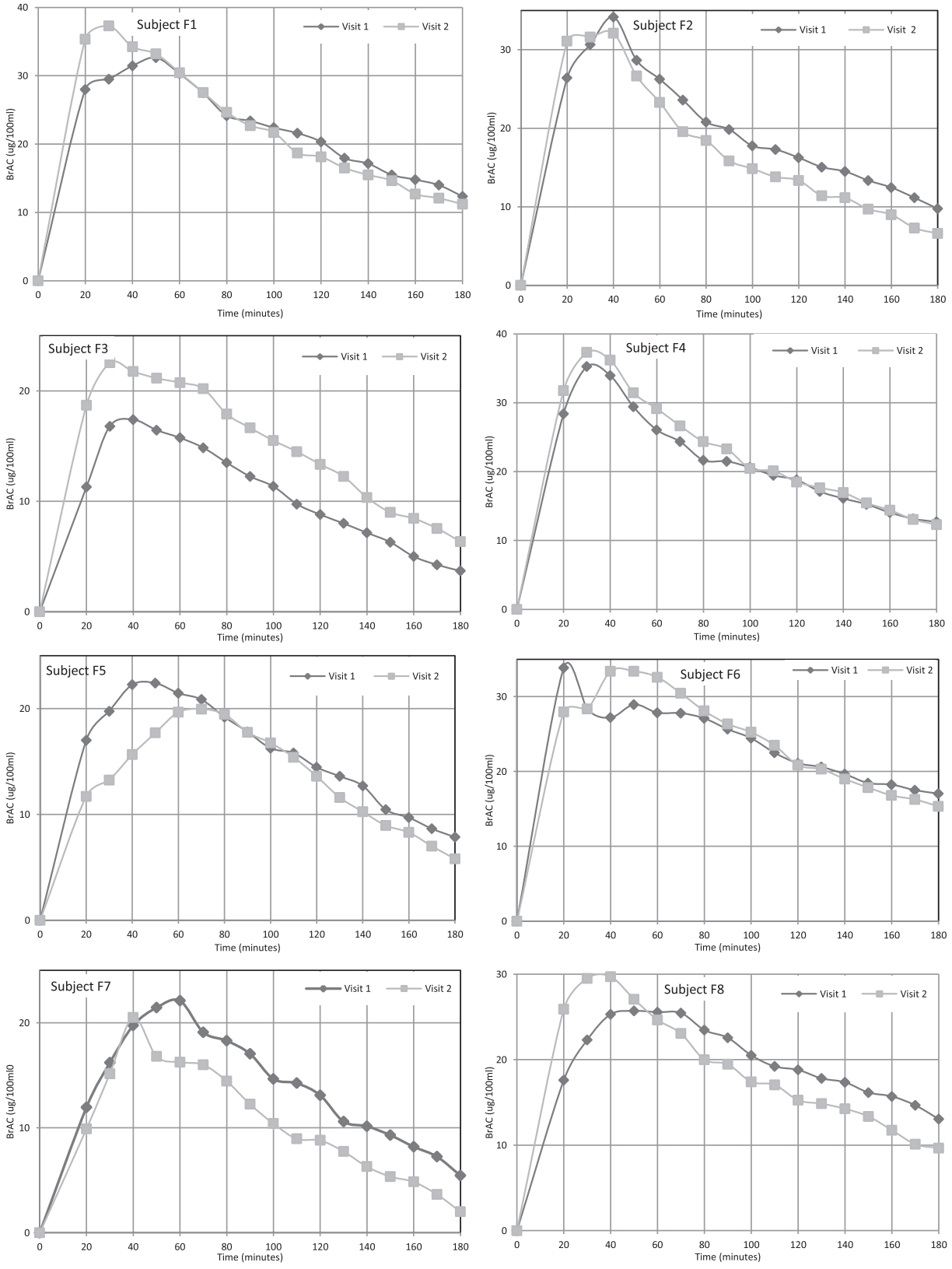

Fig. 2. Breath alcohol concentration–time curves for 8 female subjects.

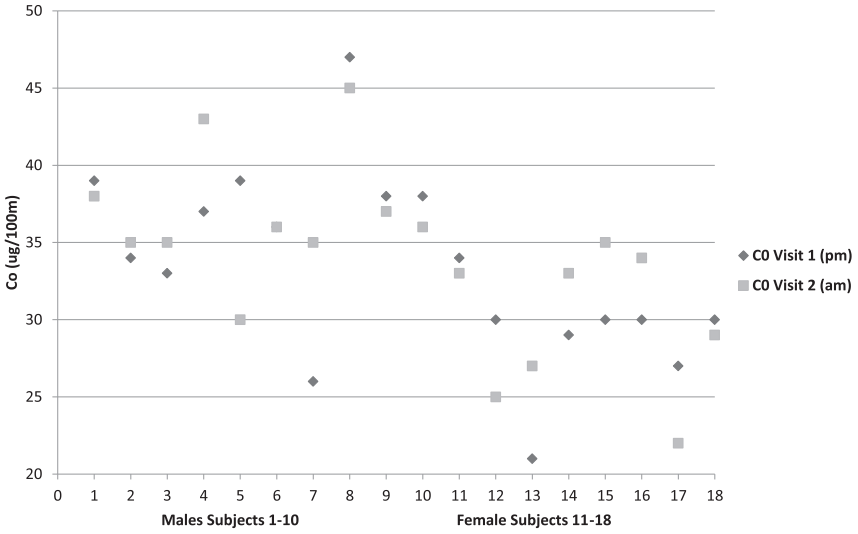

Fig. 3. C_0 extrapolated from BrAC–time curves on visits 1 & 2.

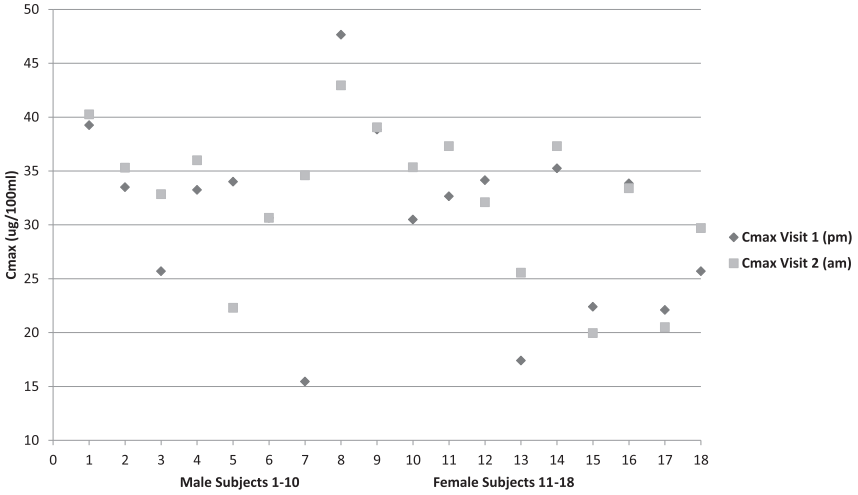

Fig. 4. Peak BrAC (C_{max}) on visits 1 & 2.

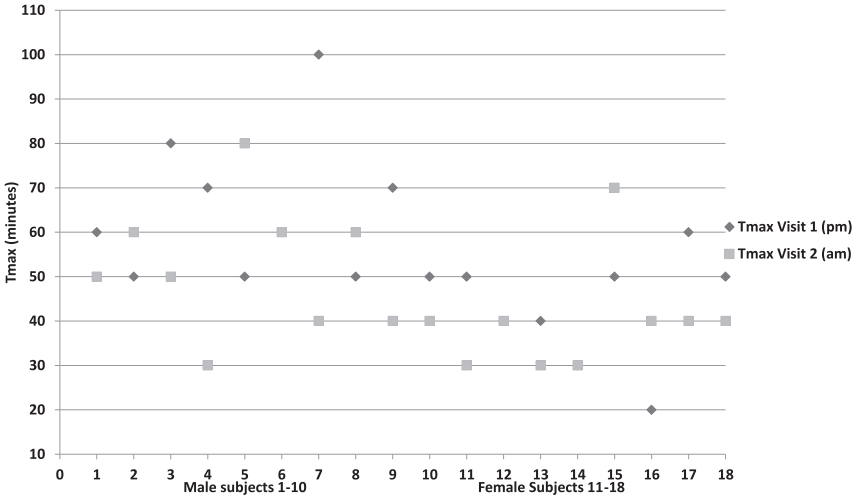

Fig. 5. Time taken to reach peak BrAC (T_{max}) on visits 1 & 2.

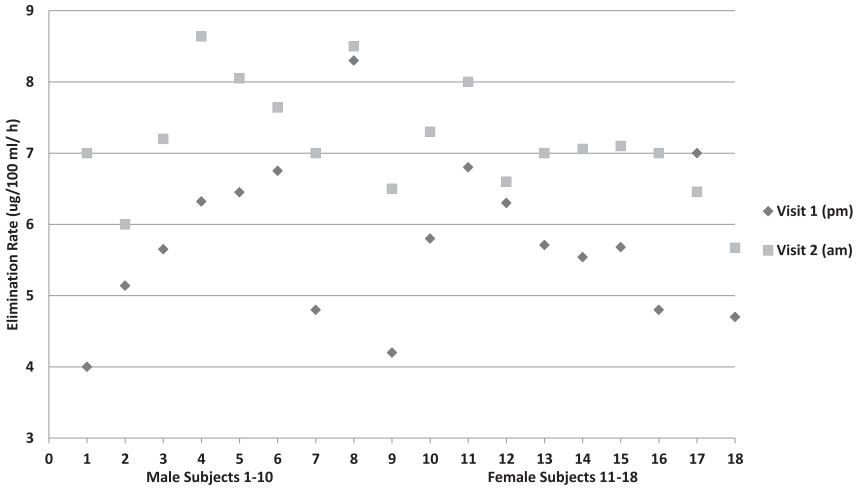

Fig. 6. Elimination rate of alcohol from breath on visits 1 & 2.

$$\text{Alcohol Dose (g)} = (\text{Target Blood Alcohol Concentration (mg/100 ml)} \times \text{Body Weight(kg)} \times r) \div 100$$

Widmark Factor (r) was calculated from simple anthropological data (height in cm (H), weight in kg (W) and Body Mass Index (W/H^2)) according to the method published by Forrest[21]:

$$\text{Fat as a percentage of body weight in males} = (1.34 \times \text{BMI}) - 12.469$$

$$\text{Fat as a percentage of body weight in females} = 1.371 \times \text{BMI} - 3.467$$

$$\text{Total Body Fat (TBF) in males} = ((1.34 \times \text{BMI}) - 12.469) \times W/100$$

$$\text{Total Body Fat(TBF)in females} = ((1.371 \times \text{BMI}) - 3.467) \times W/100$$

$$\text{Total Body Water(TBW)} = 0.724 \times (W - \text{TBF})$$

$$r = \text{TBW}/(W \times 0.8)$$

The loading dose ranged from 38 to 45 g in males and from 26 to 37 g in females. The actual volume of 12.5% white wine given (ml) = Alcohol dose (g) ÷ (0.79 × 0.125), where 0.79 is the specific gravity of alcohol (g/ml) and 0.125 represents the alcohol content of the wine by volume (12.5% abv).

2.3. Breath alcohol measurement

This bolus was consumed uniformly over a 10 min interval. BrAC measurements were performed on a Camic Datamaster Breath Analyser System, commencing 20 min after completion of drinking. The machine was set up to replicate the evidential breath testing cycle. Two breath alcohol measurements were taken in immediate succession, the second breath sample being blown immediately upon completion of the purging process after the first breath sample analysis. In practice this gave paired samples within two minutes of each other. All BrAC results were the average of these two measurements which were always within 2 units (μg/100 ml) of each other (data not shown). Serial measurements were repeated at ten minute intervals for 180 min. Throughout each experiment, subjects remained seated but were allowed to play computer games, read magazines and to chat quietly. Smoking was not permitted. Subjects were asked not to consume any more alcohol between the two visits.

2.4. Pharmacokinetic calculations

Widmark Factors were calculated for each subject according to the mathematical methods published by Watson,[19] Forrest,[21] Seidl,[22] Ulrich[23] and also calculated from the total body water

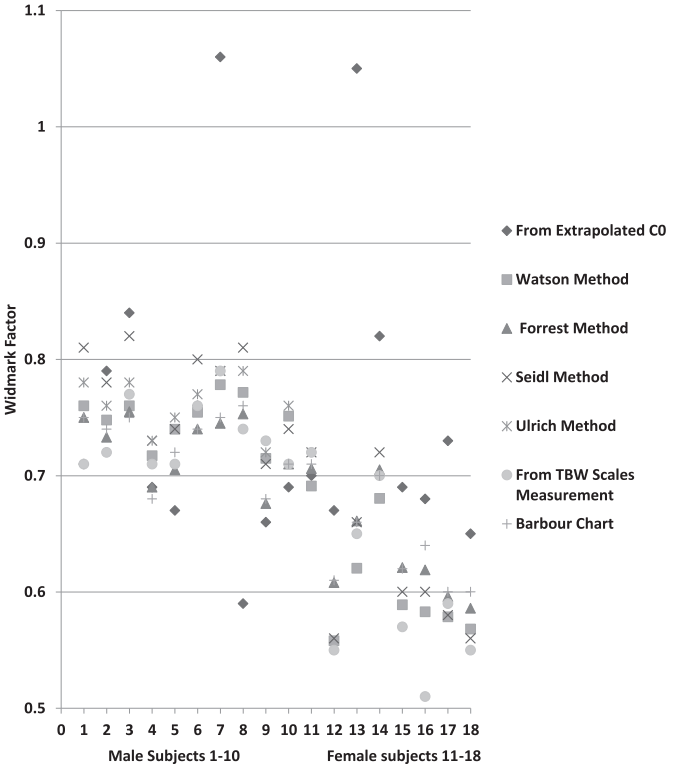

Fig. 7. Widmark Factors calculated from various measurements and mathematical methods.

measurement (measured on body composition scales), from the Widmark equation, using experimental values of C_0 extrapolated from the BrAC–time curves, and finally from the Barbour chart.[24]

Watson's method[19] for estimating total body water in an individual is based on age in years (for male subjects only), weight in kg (W) and height in metres (H):

$$\text{TBW(males)} = 2.447 - (0.09516 \times \text{Age in years}) + (0.1074 \times \text{Height}) + (0.3362 \times \text{Weight})$$

It is claimed that a simplified version is almost as accurate:

$$\text{TBW(males)} = 20.03 - (0.1183 \times \text{Age in years}) + (0.3362 \times \text{Weight}).$$

$$\text{TBW(females)} = -2.097 - (0.1069 \times \text{Height in cm}) + (0.2466 \times \text{Weight in Kg}).$$

$$\text{TBW} = 14.46 + (0.2549 \times \text{Weight})$$

$$r = \text{TBW}/\text{Weight} \times 0.8$$

The equations produced by Forrest[21] take into account variations in BMI, which generally correlate with the percentage body fat of an individual. The Barbour chart for determination of Widmark Factor is also based on the Forrest method.[24]

Seidl[22] studied a large number of subjects (256 females and 273 males), recording height in cm, weight in kg, blood water content and total body water. He updated the Widmark equation as follows.

$$r(\text{females}) = 0.31223 - (0.006446 \times W) + (0.004466 \times H)$$

$$r(\text{males}) = 0.31608 - (0.004821 \times W) + (0.004632 \times H)$$

Ulrich's research[23] was based solely on male subjects, resulting in a formula that takes into account only height and weight,

$$r(\text{male}) = 0.715 - 0.00462 \times W + 0.22 \times H(\text{in metres})$$

Statistical differences between mean values obtained on visits 1 and 2 were evaluated using the Students paired T-test function in Microsoft Excel.

3. Results

BrAC time curves for male and female subjects are presented in Figs. 1 and 2. Values of C_0, C_{max}, T_{max} and elimination rate were measured directly off the curves. Marked differences in the shape of the curves between visits may be the result of differences in completeness of fasting. Such discrepancies are most noticeable in male subjects 3, 5, 7 & 9 and female subjects 3, & 7.

Fig. 3 shows values of C_0 (extrapolated from individual BrAC curves) for each subject. The theoretical target level for males was 35 μg/100 ml breath and for females was 31 μg/100 ml breath. The figure shows quite wide and unpredictable variations in the C_0, both between individuals (inter-individual variation) and even for each individual between consecutive visits (intra-individual variation).

Fig. 4 shows the peak BrAC (C_{max}) for each subject. This shows relatively little intra-individual variation but a wide degree of inter-individual variation between subjects.

Fig. 5 shows the time taken to reach the peak BrAC (T_{max}) for each subject. This shows quite wide degrees of both intra-individual and inter-individual variation.

Fig. 6 show elimination rates measured from individual BrAC curves for each subject. This shows considerable intra-individual variation in elimination rate (from 4 to 8.6 μg/100 ml/h). Elimination appeared significantly higher ($P = 0.002$ & 0.008) on the second visit (morning) than the first visit (previous afternoon/evening). There was no significant difference in elimination rates between females and males.

Fig. 7 shows Widmark Factors calculated by various mathematical methods. Since extrapolated C_0 values were often widely different from theoretical target levels, Widmark Factors calculated from C_0 were often similarly spurious, both high and low. Widmark Factors calculated by the Watson mathematical method were mid-range in males but low range in females. The Forrest method gave values which were low range in most males but mid-range in females. The Barbour chart (which is based on Forrest's mathematical method) provides similar mid-range values in both males and females. Seidl's method gave WF values which were high range in males but low range in females. The Ulrich values were mid-range in males but calculations cannot be applied to females. Widmark Factors calculated from TBW (as measured by electronic scales) were low to mid-range in both males and females.

The pharmacological parameters are summarised in Table 2

4. Discussion

Many studies have shown that females eliminate alcohol at faster rates than males.[12–14] Kwo et al. suggests that although men and women eliminate similar amounts of alcohol per unit of body weight, females have higher liver volumes per kg of body mass and eliminate significantly more alcohol per unit of lean body mass per hour.[12] The small numbers of female subjects in the present study and the different alcohol dosages given to males and females

Table 2
Pharmacokinetic parameters of subjects.

Variable	Male subjects ($n = 10$) mean (range)			Female subjects ($n = 8$) mean (range)		
Widmark Factor (Watson)	0.75 (0.71–0.78)			0.61 (0.56–0.69)		
Widmark Factor (Forrest)	0.73 (0.68–0.76)			0.64 (0.59–0.71)		
Widmark Factor (Seidl)	0.77 (0.71–0.82)			0.63 (0.56–0.72)		
Widmark Factor (Ulrich)	0.76 (0.72–0.79)			–		
Widmark Factor (TBW Scales)	0.74 (0.71–0.79)			0.61 (0.51–0.72)		
Widmark Factor Barbour Chart	0.73 (0.68–0.76)			0.64 (0.6–0.71)		
	Visit 1	Visit 2	Difference	Visit 1	Visit 2	Difference
C_0 from curve (μg/100 ml)	36.7 (26–47)	37 (30–45)		28.9 (21–34)	29.8 (22–35)	
% of predicted C_0	105% (74–134)	105% (86–129)		93% (68–110)	96% (71–113)	
C_{max} (μg/100 ml)	32.9 (15.5–47.7)	34.9 (22.3–43)		27.9 (17.4–35.3)	29.5 (20–37.3)	
T_{max} (min)	64 (50–100)	51 (30–80)	NS	42.5 (20–60)	40 (30–70)	NS
β Elimination from breath (μg/100 ml/h)	5.7 (4–8.3)	7.4 (6–8.6)	$P = 0.002$	5.8 (4.7–7)	6.9 (5.7–8)	$P = 0.008$
WF (from C_0)	0.75 (0.59–1.06)	0.73 (0.59–0.86)	NS	0.75 (0.65–1.05)	0.72 (0.58–0.88)	NS

preclude any meaningful comparison of elimination rates between the two sexes.

The quoted average rate of alcohol elimination from blood of 15 mg/100 ml/h is equivalent to a breath elimination rate of 6.5 μg/100 ml/h. Our results suggest that alcohol is eliminated from breath at slightly higher rates in the morning than the previous evening in both males (7.4 versus 5.7 μg/100 ml/h) and females (6.9 versus 5.8 μg/100 ml/h). Yap demonstrated slightly higher peak levels attained at 9 a.m. than in other sessions throughout a 24 h period but no diurnal variation in other pharmacokinetic parameters, including elimination rate.[11] Further work is required to determine what factors affect elimination and their time course.

It is possible that differences in the shape of BrAC–Time profiles and elimination rates may relate to different degrees of fasting. Subjects are more likely to present in a more completely fasted state in the morning (having fasted overnight) than in the afternoon when there has been greater temptation and opportunity to eat during the day. Suspicion is aroused when the BrAC–time curves differ markedly in shape between visits (as seen in Fig. 1 for male subjects 3, 5, 7,& 9 and Fig. 2 for female subjects 3 & 7).

Our results show that values of C_0 measured from the BrAC–time curves showed considerable inter-individual variation (Fig. 3). Since C_0 is inversely proportional to WF, values of WF obtained from the BrAC curves were also much more variable than those which were mathematically predicted from sex, weight, height and age.

In general, the Widmark Factors determined by various mathematical methods in our subjects were mostly higher than the quoted mean values of 0.68 for males and 0.55 for females. This is not unexpected since the subjects chosen for this study were mostly fit young students with lean body mass and therefore high Widmark Factor. In medico-legal situations, it is preferable to use one of the mathematical methods to predict an individual's Widmark Factor, rather than use the original quoted mean values of 0.68 for males and 0.55 for females. In our subjects, Watson's method provided low values of WF in females (compared to other methods) and Seidl's method provided high values in males. In practice, the Forrest method and the Barbour chart seem to provide the most consistently accurate predictions in both males and females. The Barbour chart has the added advantage of simplicity in use.

The degree of inter-individual and intra-individual variation in elimination rate and other pharmacokinetic parameters seen in this study, occurring even within the course of 24 h, may have an important bearing on the application of alcohol elimination rates in medico-legal situations.

Ethical approval

Ethical approval granted by Tayside Research Ethics Committee.

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None declared.

Conflict of interest

No conflicts of interest were identified by either of the authors in the preparation and submission of this article.

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